Amendment to the Drawings:

The attached sheet of drawings includes changes to Figures 1, 2, 3, and 4. This sheet, which includes Figures 1, 2A, 2B, 3A, 3B, 4A and 4B replaces the original sheets including Figures 1, 2, 3, and 4.

Attachment: Replacement Sheets

REMARKS/ARGUMENTS

In the specification, paragraphs [0013], [0014] and [0015] have been amended to reflect the amendments made to the drawings, discussed in more detail *infra*. New paragraphs [0013], [0014] and [0015] include no new material. Paragraphs [0023] and [0038], as published, have been amended to correct minor informalities and include no new material.

Claims 1-5, 7-31 and 40-69 are pending in the application. Claims 1-21 and 27-69 have been canceled. Claims 22-26 have been withdrawn as the result of an earlier restriction requirement. In view of the Examiner's earlier restriction requirement, Applicant retains the right to present claims 22-26 in a divisional application. Claims 70-87 are newly added. Support for the new claims can be found, for example, in the specification, as published, in paragraph [0020], lines 5-8; paragraph [0022], lines 1-2; Example 1, beginning with paragraph [0028]; and, Example 2, beginning with paragraph [0040].

Drawings

New corrected drawings in compliance with 37 C.F.R. § 1.121 (d) are required in this application because the drawings are of insufficient quality. New drawings 1, 2A, 2B, 3A, 3B, 4A and 4B replace original figures 1, 2, 3, and 4. The new Figure 1 replaces the original Figure 1 and includes no new material. Figures 2 through 4 have each been replaced with A and B versions of the same drawings. Original Figures 2, 3 and 4 each included four graphs depicting the before and after sterilization volume percent particle size distribution for each batch. New Figures 2A, 2B, 3A, 3B, 4A and 4B replace original Figures 2, 3 and 4 and depict the "before sterilization" volume percent particle size with and without a cold pack in Figures 2A, 3A and 4A, and the "after sterilization" volume percent particle size with and without a cold pack in Figures 2B, 3B and 4B. No new material has been included in any of the drawings.

35 U.S.C. §112 Rejections

Claims 42-69 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Specifically, the Office rejected claims 42-49 because "suspended in an emulsion" was not disclosed in the original application. Claims 42-49 have been canceled and the new claims do not recite "suspended in an emulsion." As such, this rejection is now moot.

Claims 42-46 are rejected for reciting a percentage of microparticles not in contact with other microparticles, which is an impossible percentage to determine from the specification or drawings. Claims 42-46 have been canceled and the new claims do not recite a percentage of microparticles not in contact with other microparticles. As such, this rejection is now moot.

Claims 47-49 are rejected for reciting a percent change in diameter after irradiation which cannot be gleaned from the specification or drawings. Claims 47-49 have been canceled and the new claims do not recite a percent change in diameter. As such, this rejection is now moot.

The Office rejected claims 50-67 for the same issues as those cited for claims 47-49 and additionally for reciting sterilized material that need not be irradiated. Claims 50-67 have been canceled and the new claims do not recite a percent change in diameter or sterilized material that need not be irradiated. As such, this rejection is now moot.

Claims 68-69 are rejected for reciting a product that has microparticles which are less aggregated than those which are irradiated at 25°C. In the Office's now moot rejection, the Office stated that because the specification only shows a decrease in aggregation when irritated at less than 5°C in the examples, that the "comparison-type" claims are new matter. Claims 68-69 have been canceled and as such, this rejection is now moot.

Claims 1-5, 7-21, and 40-69 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for the microparticles and the active agent shown in the examples of the specification, it does not reasonably provide enablement for any other polymeric microparticle, or the microparticle of the specification in combination with other active agents. Claims 1-5, 7-21, and 40-69 have been canceled and therefore, this rejection is now moot.

However, as to new claims 70-87 the Applicants respectfully assert that the science of polymer chemistry and controlled therapeutic drug delivery using polymeric materials is a well developed art. It is well established that a patent specification need not teach, and preferably omits, what is well known in the art. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367. In the present case, methods for optimizing polymer/therapeutic mixtures and adjusting their controlled release profiles are well known in the art. See for examples, Pillai, O. Curr Opin Chem Biol. 2001 Aug;5(4):447-51; "Polymers in Drug Delivery" by Ijeoma F. Uchegbu (Editor), Andreas G. Schatzlein (Editor) CRC Press, 2006; Dirk Schmaljohann, "Thermo- and pH-responsive polymers in drug delivery", Advanced Drug Delivery Reviews, Volume 58, Issue 15, 30 December 2006, Pages 1655-1670, 2006 Supplementary Non-Thematic Collection. See also United States patent numbers (as a mere sampling of over 12,731 hits identified using the search terms "polymer and "controlled release" on the USPTO search engine) 5,487,895; 6,419,949; 6,428,780 and 6,503,528.

Persons of ordinary skill in the art, as exemplified by the expert publications cited *supra*, would be able to make myriad different polymer/therapeutic combinations using known and well published techniques. Then, applying the detailed and highly enabled teachings of the Applicants' present specification, each polymer/therapeutic combination could, using routine experimental techniques, be systematically tested to ascertain desirable physical parameters, such as particle shape, size and percent aggregation. This information, based on the present teachings, would then be used to determine which polymer/therapeutic combinations were best suited for a specific application. Therefore, the Applicants respectfully assert that the Office cannot

substantiate a new 35 U.S.C. §112, first paragraph rejection against claims 70-87 similar to the one asserted against now canceled claims 1-5, 7-21 and 40-69, nor can the Office properly assert that the present specification is not enabled for polymeric compounds and therapeutic agents other than those used in specific embodiments disclosed in the present application.

Claims 1-5, 7-21, and 40-67 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Particularly, claims 1 and 59 and all dependent claims are rejected because the specification does not disclose how little aggregation is allowed for the particles to be "substantially non-aggregated" as claimed. Claims 1-5, 7-21, and 40-67 have been canceled and the new claims do not recite particles that are "substantially non-aggregated." As such, this rejection is now moot.

35 U.S.C. §102 Rejections

Claims 1-5, 7-12, 16-21, 27-31, and 40-69 are rejected under 35 U.S.C. § 102(b) as being anticipated by United States Patent Number 4,835,139 to Tice et al. ("the Tice reference") and by United States Patent Number 5,534,261 to Rodgers et al. ("the Rodgers reference") for reasons of record. Particularly, the Office notes that the microparticles disclosed in the present specification are not the same as the particles in Tice and Rodgers and as such, more information is necessary to determine whether or not the results disclosed in this application are also generally applicable to other microparticle. Claims 1-5, 7-12, 16-21, 27-31, and 40-69 have been canceled and as such, this rejection is now moot.

Furthermore, the Applicants respectfully assert that in light of the new claims, the subject matter of the current application is not anticipated by the Tice or the Rodgers references. The Office Action mailed August 9, 2007 concludes that microparticle aggregation is unpredictable because particle size before and after irradiation, as depicted in Montanari et al. ("the Montanari reference"), does not follow a predictable

pattern. The Office applies this conclusion to the Tice and Rodgers references to surmise that the results disclosed in the current specification will not apply generally to all microparticles, and as such, they do not overcome a prior anticipation rejection over Tice and Rodgers.

However, this conclusion is based on the incorrect assumption that particle size and particle aggregation are correlated. As shown in figures 2B, 3B, and 4B of the present application, the diameter sizes of microparticles sterilized at room temperature vary greatly. The diameter sizes of the room-temperature sterilized microparticles can vary from diameter sizes similar to those of the pre-sterilized microparticles to diameter sizes one thousand times larger. This variance is not seen with the microparticles irradiated at less than 25°C.

Further, the variance seen with diameter size after gamma-irradiation at room temperature is not seen in particle aggregation after gamma-irradiation at room temperature. As shown in Figure 1 of the current disclosure, substantial aggregation was observed with both drug loaded and unloaded microparticles gamma irradiated at 25°C, but not with the microparticles irradiated at less the 25°C. Figure 1 demonstrates noticeable aggregation in all three batches sterilized at room temperature, and little to no aggregation in all three batches sterilized at less than 25°C.

The combination of results disclosed in Figures 1 through 4 of the current application clearly demonstrates the lack of correlation between particle size and particle aggregation after irradiation, at room temperature. Therefore, the Office has wrongly assumed the correlation between particle size and aggregation and has wrongly concluded it as the basis of this rejection.

The Tice and Rodgers references do not disclose gamma-irradiated microparticles that are less aggregated when irradiated at temperatures less than 25°C than at temperatures more than 25°C. Further, the Tice and Rodgers references do not teach the variance in irradiation temperature, the beneficial qualities of lower irradiation temperatures, or the comparison of aggregated microparticles at irradiation

temperatures less than and greater than 25°C. As such, neither the Tice reference nor the Rodgers reference discloses each and every limitation of the present claims.

Claims 1-5, 7-12, 16-21, 27-31, and 40-69 are rejected under 35 U.S.C. § 102(b) as being anticipated by Montanari et al. "Gamma irradiation effects on the stability of poly(lactide-co-glycolide) microsphere containing clonazepam" ("the Montanari reference"). Particularly, the Office argues that the Montanari reference teaches PLGA microspheres containing clonazepam and irradiated with gamma-radiation, and that the particles do not aggregate to any significant extent upon irradiation. Claims 1-5, 7-12, 16-21, 27-31, and 40-69 have been canceled and as such, this rejection is now moot.

Further, the Applicants respectfully assert that in light of the new claims, the subject matter of the current application is not anticipated by the Montanari reference. The present claims teach that gamma-irradiated microparticles are less aggregated when they are gamma-irradiated at less than 25°C than when they are irradiated at greater than 25°C. The Montanari reference discloses PLGA microspheres that have been gamma-irradiated at room temperature. The Montanari reference does not measure the aggregation of the microparticles and does not teach any correlation between particle aggregation, particle size or the gamma-irradiation temperature. The Office cites sections 2.2, 3.1, and Figure 2 to show that the microspheres do not aggregate to any significant extent upon irradiation. However, sections 2.2, 3.1 and Figure 2 disclose the particle diameter size with and without irradiation at different frequencies at room temperature. As discussed *supra*, particle aggregation and particle size are not correlated and therefore, it cannot be assumed that the disclosed particle diameter size in the Montanari reference can be used to predict the amount of particle aggregation.

Additionally, the Montanari reference does not teach variance in irradiation temperature, the beneficial qualities of lower irradiation temperatures, or the comparison of aggregated microparticles at irradiation temperatures less than and greater than 25°C. As such, the Montanari reference does not teach each and every limitation of the present claims.

35 U.S.C. §103 Rejections

Claim 15 remains rejected under 35 U.S.C. § 103(a) as being unpatentable over United States Patent Number 5,534,261 to Rodgers et al. in view of United States Patent Number 6,365,623 to Perricone for reasons of record. Specifically, the Office rejects claim 15 as being obvious in light of the Rodgers reference, which teaches sterile microparticles made of polyactide-glycolide copolymers comprising retinoids, and the Perricone reference, which teaches tazarotene as a widely recognized retinoid. Claim 15 has been canceled and resultantly, this rejection is now moot.

Furthermore, the Applicants respectfully assert that the Office has not met its burden of establishing a *prima facie* case of obviousness and has not shown that the combination of the Rodgers and Perricone references teaches or suggests the subject matter of this application. As discussed in detail *supra*, the Rodgers reference does not disclose, as does the present disclosure, gamma-irradiated microparticles that are less aggregated when irradiated at temperatures less than 25°C than at temperatures more than 25°C. Moreover, the Rodgers reference does not teach the variance in irradiation temperature, the beneficial qualities of lower irradiation temperatures, or the comparison of aggregated microparticles at irradiation temperatures less than and greater than 25°C. Additionally, the Perricone reference does not cure the deficiencies in the Rodgers reference, and the combination of the Rodgers and Perricone references do not teach or suggest the subject matter of the new claims and the present application.

Applicants respectfully request that a timely Notice of Allowance be issued in this case.

The Commissioner is authorized to charge any fee which may be required in connection with this Amendment to deposit account No. 50-3207.

Respectfully submitted,

Dated: 09jan07

Joseph Taffy
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